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Invited Review

Fibromyalgia: Update on Pathogenesis and Management

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Abstract

Fibromyalgia (FM) is a complex disorder characterized by chronic widespread pain, fatigue, sleep disturbances, mood alterations, and cognitive impairment. This review aims to provide an updated understanding of pathophysiology and management, highlighting recent advances in both pharmacologic and non-pharmacologic treatment options. Multifactorial pathophysiology includes the central and peripheral nervous systems, psychosocial stressors, the hypothalamic–pituitary–adrenal axis, the autonomic nervous system, and the immune system. Obesity and obstructive sleep apnea are also significant contributors. Diagnosis is clinical and requires a systematic approach. Non-pharmacologic treatments, including education, psychotherapy, exercise, and sleep optimization, are first-line management. Pharmacotherapy is offered to patients who need additional symptom control, and evidence for the most promising options is discussed. The review underscores the importance of a multidisciplinary approach to improve quality of life and suggests potential future directions for FM management.

Keywords: Fibromyalgia, nociplastic, pain, serotonin, pregabalin, naltrexone

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Introduction

Fibromyalgia (FM) is a nociplastic disease of protean manifestations which has frustrated patients and challenged rheumatology, neurology, primary care, and rehabilitation communities for decades. Recently, significant advances have been made in our understanding of the multifactorial and eminently complex pathophysiology of this debilitating widespread pain disorder. Similar progress has been made in treatment options, both pharmacologic and non-pharmacologic. The aim of the present review is to introduce pathophysiology, clinical manifestations, and diagnosis, as well as current evidence-based treatment options, both pharmacologic and non-pharmacologic. The authors also hope to provide insight into and stimulate discussion of potential future directions for therapy based on new treatment options heretofore underutilized or not even considered in FM management. The authors hope to appeal to primary care as well as specialty audiences, with a discussion of current options and future directions for multidisciplinary care.

Epidemiology

Fibromyalgia is the third most common musculoskeletal disorder following low back pain and osteoarthritis. The estimated worldwide prevalence of FM is in the range of 2-3%.[1] The overall prevalence is 2-8% in the US, with estimates depending on criteria applied, while overall prevalence in the population of 5 European countries was recently found to range from 2.9% to 4.7%, depending again on criteria used. The most common onset is at the beginning of the fourth decade of life, with highest prevalence in the sixth decade.[1,2] Fibromyalgia expression demonstrates a female-to-male ratio of approximately 2 : 1, though this also depends on diagnostic criteria used, with older criteria giving a higher ratio.[3] The prevalence also comes with a cost to society, in both healthcare expenditures and lost productivity.[4] An even greater portion of the population has chronic widespread pain. One UK survey estimated that 14% of the population has chronic pain and only 5% met criteria for FM.[5]

Clinical Manifestations

Fibromyalgia is a heterogeneous condition characterized by chronic widespread pain (CWP) associated with fatigue, sleep disturbances, mood alterations, and/or cognitive impairment, among other symptoms. The presentation can be highly variable and overlap with other conditions including other pain disorders, complicating diagnosis. It often takes years to reach a diagnosis as patients present with a combination of system involvement.[6] Fibromyalgia can coexist with the full spectrum of systemic autoimmunity, often emerging after the canonical inflammatory disorder has taken hold.

Musculoskeletal: Diffuse, widespread pain may involve essentially any part of the musculoskeletal system including the chest, abdomen, and pelvis.

Sleep-related: Fatigue and disruptions in sleep are key features. Patients report severe, persistent fatigue often worsened with minimal activity. Patients may report poor sleep or waking unrefreshed. There is commonly co-occurring OSA. An elegant but small 2017 study of 24 patients with FM detected OSA in 50%.[7]

Neurological: Patients may experience multifocal paresthesia, recurrent headaches, and autonomic dysfunction. Cognitive disturbances are also common.

Psychological: Manypatients have co-morbid mood disorders.[8]

Gastrointestinal: Abdominal pain, bloating, gas, recurrent diarrhea, and/or constipation consistent with irritable bowel syndrome are common symptoms. Gastroesophageal reflux disease is also often extant.[9,10]

Pathophysiology

The pathophysiology of FM remains elusive, but a hypothesis of multifactorial causation continues to gain support. Specifically, FM results from interplay of the central nervous system (CNS), the peripheral nervous system (PNS), psychosocial stressors, the hypothalamic–pituitary–adrenal (HPA) axis, the autonomic nervous system, and the immune system.[1,11] Other active contributors to pathology include sleep dysfunction and psychological disorders.[1] The authors suggest that obesity also plays a pathologic role in a significant proportion of patients not only because of an epidemiological association but because of the association of elevated interleukins IL-6 and IL-8 with both obesity and FM. Figure 1 provides an overview of putative multifactorial causation in FM (Figure 1).

Main Points

- Fibromyalgia is a nociplastic pain disorder with a complex, multifactorial pathophysiology.
- Central sensitization potentiated by nociceptive stimuli and an inflammatory process is central to FM pathogenesis.
- There are several variably effective non-pharmacologic and pharmacological treatments available for FM, some of which target established pathologic processes.
- Multimodal and multidisciplinary treatment optimizes outcomes in FM to the extent currently possible.

Fibromyalgia as a Disorder of Nociplastic Pain

A third pain mechanism termed "nociplastic" was introduced in 2016, as distinct from nociceptive and neuropathic pain. The International Association for the Study of pain defines nociplastic pain as "pain that arises from altered nociception despite no clear evidence of actual or threatened tissue damage causing the activation of peripheral nociceptors or evidence for disease or lesion of the somatosensory system causing the pain."[12] Such pain can occur alone or concurrently with one of the other pain mechanisms.

Nociplastic pain disorders bear the following characteristics: The pain is widespread and is associated with fatigue, memory, sleep, and mood problems. Risk factors include genetics as well as adverse childhood experiences, early and late trauma, and multi-comorbidity among others. There are multiple mechanisms at play centrally and peripherally, with the CNS largely maintaining nociplastic pain, while being potentiated by peripheral nociceptive stimulation. There is immune system activation in these syndromes, but inflammation is limited to certain cytokines identified in CSF and serum studies and is not considered to extend to canonical autoimmunity. Fibromyalgia is a prototypical nociplastic pain disorder.[13]

Central Sensitization and Inflammation

Fibromyalgia shares a central sensitization component with several other diseases including rheumatoid arthritis and osteoarthritis. A recent review proposed there are multiple central sensitization phenotypes and that further identification and sorting could eventually guide "precision pain medicine treatment."[14] Recently, a retrospective study of 265 patients with FM suggested an association between central sensitization and both neuropathic pain and small-fiber neuropathy.[15]

Dysfunction of neurotransmitter metabolism leading to increased excitation and decreased inhibition results in central sensitization. Anomalous neurotransmission is felt to be potentiated by inflammatory processes in the nervous system marked and possibly mediated by IL-6 and IL-8.[11] Neuroinflammatory processes in both CNS and PNS have been correlated with disease activity in FM.[16]

Pain in FM is accompanied by activation of immune cells including microglia and mast cells which in turn secrete neuroactive cytokines and chemokines that potentiate the snowball effect of central sensitization.[1,17] Indeed, there is increasing support for neural-based inflammation in both CNS and PNS as potentiating FM. Studies have found increased IL-8 in CSF of patients with FM relative to controls, as well as increased serum IL-1 beta, IL-6, IL-8, and tumor necrosis factor (TNF) alpha in patients with FM. Animal studies have demonstrated the ability of pro-inflammatory cytokines to activate and sensitize nociceptors.[18]

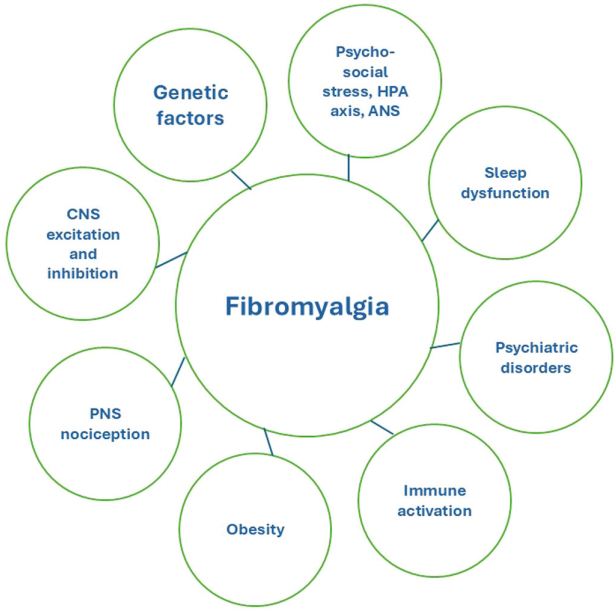

Figure 1. Putative multifactorial causality in fibromyalgia. HPA, hypothalamic, pituitary, adrenal; ANS, autonomic nervous system; PNS, peripheral nervous system; CNS, central nervous system.

Dr. Gonzales-Alvarez' group recently studied women with FM in Madrid during 2023, including IL analysis on 30 patients. They showed IL-6 elevation in association with higher FIQ (Fibromyalgia Impact Questionnaire) scores, corresponding to worse disability. Furthermore, they found IL-8 elevated in connection with increased pain intensity and functional impairment. These findings support a link between systemic inflammation and worse clinical outcomes. Taken together with previous studies, their findings support a role for IL-6 and IL-8 as not only biomarkers for disease activity but as potential therapeutic targets.[19]

Excitatory and Inhibitory Pathways

Nociception, perception of pain, is a function of ascending and descending pathways. Nociceptive input is transferred to the CNS via afferent neuronal pathways. In a parallel but dissimilar fashion, descending inhibitory input modulates nociception.[20] Neurokinins A and B plus substance P, as well as glutamate, have been implicated in the excitatory pathway of FM pathophysiology.[16,20] There is increased spinal cord neuronal sensitivity which is mediated in large part by the N-methyl-D-aspartate receptor (NMDAR). The NMDAR is a glutamate receptor that mediates excitatory neurotransmission. Evidence for its involvement in FM is provided by imaging studies showing elevated glutamate levels in brain tissue of patients with FM. The effectiveness of NMDAR antagonists, to be discussed below, further implicates this pathway as pathological.[20,21]

Inhibitory pathways are mediated by opioid, 5-hydroxytryptamine-1A, and alpha-2-adrenergic receptors along with gamma-aminobutyric acid receptors. It has been suggested that alterations of physiologic inhibitory tone are pathologic.[20] Studies suggest normal to increased endogenous opioid tone in patients with FM, which reflects high occupancy of mu-opioid receptors. This begins to explain why patients might benefit from low-dose naltrexone.[13,16] The noradrenergic and serotoninergic pathways have been postulated to be involved in both ascending and descending nociceptive pathways, suggesting FM pathophysiologic commonality with that of depression. Studies have shown FM patients have decreased serotonin, norepinephrine, and tryptophan levels in serum. Additionally, the serotonin metabolite, 5-hydroxyindoleacetic acid, and norepinephrine metabolite 3-methoxy-4-hydroxyphenethylene are reduced in CSF. This might explain the benefit of serotonin-norepinephrine reuptake inhibitors (SNRIs) for both FM and depression.[16,20]

Genetic Factors

Polymorphisms in genes regulating catecholamine metabolism have been associated with FM. Both catechol–o–Methyltransferase and 5-hydroxytryptamine receptor 2A have been implicated.[11] Other polymorphisms have been identified in at least 27 genes regulating the pain pathway, as to modulation, perception, transmission, and transduction. These have been correlated with specific phenotypic effects in FM in myriad studies.[11,22]

Early evidence suggests the inflammation in FM may have a genetic and epigenetic basis. There are associations of DNA methylation with FM development. Variable gene expression almost certainly plays a role in pathogenesis.[11] Recent evidence of a locus being identified as associated with CWP was put forth in a large genetic study implicating polymorphism at the Ring Finger 123 locus.[23] Finally, a familial component to FM pathophysiology is supported by a large genome wide association study.[24]

Psychosocial Factors, Hypothalamic–Pituitary–Adrenal Axis, and Autonomic Nervous System

There is a clear link between exposure to early stressors and FM. Studies on human stress systems have consistently shown HPA axis and sympathetic nervous system alterations in FM and related syndromes. Evidence also shows that these abnormalities may be to some extent secondary to the peripheral nociception. The HPA axis is crucially involved in central sensitization, given it controls the response to stress, mediated initially by corticotropin-releasing hormone, which precipitates glucocorticoid release and immune modulation.[1,16]

Obesity

A systematic review of 41 studies found an overall prevalence of obesity in FM of 35.7% worldwide and 43% in the US. Overall, the analysis supports a role for obesity in precipitating and maintaining FM symptoms. They hypothesize that obesity potentiates FM by mechanical overload of joints, tendons, and muscles, including microscopic changes associated with obesity. Additionally, the authors have previously discussed that FM is characterized by inflammatory milieu in cerebrospinal fluid (IL-8) and serum (IL-1 beta, IL-6, IL-8, and TNF alpha). Although inflammation may or may not be a key mechanism in FM, in obese patients, it may play a more significant role given increased adipocyte release of monocyte chemoattractant protein-1, which recruits monocytes to adipose tissue and favors differentiation to a macrophage phenotype that produces TNF alpha, IL-6, and IL-1 beta. These go on to sensitize peripheral nociceptors. Both obesity and FM share symptoms of fatigue, exercise intolerance, depression, and cognitive dysfunction, and there is a complex interplay where obesity may not only represent an aggravating factor but also a potential trigger of FM.[25]

Obstructive Sleep Apnea

Obstructive sleep apnea has a strong association with FM, possibly being causal. A recent single-center retrospective analysis suggested a correlation between the 2 disorders but not necessarily a causal relationship.[26] Other recent evidence of this relationship is a cross-sectional study of 38 female patients with FM presenting to a physical therapy outpatient clinic found that 65.9% of comers also had OSA by standard criteria.[27]

Diagnosis

Current Diagnostic Criteria

The diagnosis of FM is clinical, and diagnostic criteria have evolved over time. The most recent revision of the American College of Rheumatology (ACR) criteria shifted away from the prior tender point criteria. According to the ACR 2016 revision, a patient satisfies diagnostic criteria for FM if the following 3 conditions are met with a final caveat: First, the patient has pain in at least 4 of 5 regions. Secondl, the symptoms must have been "present at a similar level" for at least 3 months. Third, the patient shows a WPI (widespread pain index) of 7 or greater and SSS (symptom severity scale) score of 5 or better or WPI 3-6 and SSS score of 9 or greater. Finally, the patient may be diagnosed with FM in the presence of virtually any other clinically significant diagnosis.[28,29]

Evaluation

A systematic approach is needed to exclude alternative causes of pain as many FM symptoms overlap with other chronic pain and inflammatory disorders. Pain is the dominant symptom in FM. However, other symptoms such as fatigue, unrefreshed sleep, mood disturbance, and cognitive impairment are common, but not universal, and have an important influence on quality of life in this heterogenous condition.[6]

Clinical evaluation includes a comprehensive history and physical with attention to the revised 2016 diagnostic criteria. The evaluation should include musculoskeletal and psychiatric evaluations, relevant labs and imaging of any tender and/or swollen joints. Testing should include an evaluation of kidney, liver, and thyroid function, a complete blood count,

25-hydroxy-vitamin D, and a urinalysis.[6,30] Muscle enzymes and inflammatory markers (c-reactive protein and erythrocyte sedimentation rate) should be sent to assess muscle and systemic inflammation, respectively. Serologies may be sent to diagnose or exclude the full spectrum of systemic autoimmune diseases as guided by history and physical. In our experience, there is no downside to a comprehensive lab work-up for the patient ultimately diagnosed with FM. Moreover, if the patient is experiencing symptoms of sleep apnea, a sleep study is warranted.[7]

Differential Diagnosis

Fibromyalgia shares symptoms with many chronic conditions. Key conditions to consider in the differential include, but are not limited to, myalgic encephalomyelitis-chronic fatigue syndrome, complex regional pain syndrome, and primary neurologic disorders such as MS, systemic autoimmune disorders, osteoarthritis, and post-viral syndromes.

The diagnosis of FM remains challenging, particularly in primary care settings, due to its complex symptom profile, frequent overlap with other conditions, and historical mischaracterization as a psychosomatic disorder. These factors contribute to underdiagnosis and inconsistent treatment. The absence of a specific biomarker mandates careful differentiation from other inflammatory, neurological, and psychiatric conditions.[30]

Nonpharmacologic Treatment

The treatment of FM is multi-faceted and individually tailored. First-line treatments for FM are non-pharmacologic, including education, psychotherapy, attention to sleep, and exercise. Indeed, "the core tenets of treating nociplastic pain are to get individuals moving and sleeping."[13] Because FM encompasses such a broad range of disturbances in addition to pain, interventions aimed at good-quality sleep, optimal mood, exercise, and nutrition may be adequate in improving quality of life. If necessary, pharmacotherapy can be added.

Education

Education emphasizes evidence-based knowledge of the condition along with optimization of lifestyle practices.[30] Educating patients on the physiological mechanism of pain has been shown to lower pain and increase well-being compared to those who only receive management instructions.[31]

Psychological Therapies

While many different psychotherapeutics (hypnosis, cognitive behavioral therapy (CBT), and mindfulness-based stress reduction) have been studied in chronic pain and FM, there is only high-quality evidence for efficacy of CBT to reduce FM symptoms and disability.[32] Cognitive behavioral therapy has also been shown to improve sleep in patients with chronic pain.[33] Supportive therapy with empathic responding is generally of benefit to patients with FM, as with any chronic illness affecting biopsychosocial functioning.

Pain reprocessing therapy (PRT) is a novel psychotherapy aimed at altering pain perception through mechanisms including pain reappraisal, fear reduction, and exposure-potentiated extinction. One study in patients with chronic low back pain showed significant and sustained pain reduction.[34] Given a substantial benefit evident for chronic low back pain, and from our own clinical experience, the authors suspect PRT has a similar benefit in other nociplastic pain conditions such as FM.

Acupuncture

Acupuncture has been shown to somewhat improve pain and fatigue in women with FM. A meta-analysis found it improved overall pain but was only clinically significant when combined with exercise and pharmacotherapy.[35] A more recent review showed evidence for reduction in pain thought to be partly due to interplay of other ameliorating factors.[36]

Transcutaneous Electrical Nerve Stimulation

Transcutaneous electrical nerve stimulation (TENS) is a safe and inexpensive therapy that modulates inhibitory mechanisms of analgesia. Additionally, TENS has been shown to be a safe adjunctive treatment in patients on an opioid regimen.[37] There is a paucity of evidence supporting benefit in FM.

Exercise

A 2017 Cochrane review found moderate-quality evidence that aerobic exercise probably improves health-related quality of life, and low-quality evidence that aerobic exercise may slightly decrease pain intensity as well as slightly improve physical function.[38] Regarding resistance training, a 2024 meta-analysis found that compared with other exercises, it demonstrated a favorable effect on FIQ total score, with comparable effects on pain control, tender points, physical function, and depression.[39]

Yoga is a form of mindful exercise, often employed in a group setting, and the social connection may be of benefit to FM patients. There are studies showing modest benefits of yoga in FM, specifically as to improve pain, mood, fatigue, mood, and coping strategies.[40,41]

Pharmacologic Treatment

Patients who do not achieve adequate disease modulation from the above interventions may benefit from pharmacologic therapies to further augment disease control. In general, patients diagnosed with FM will cycle through a number of treatments until one is found that is even moderately effective. Such is the current state of our therapeutics for FM. In our experience, a 4-6-week trial of a given medication is warranted to determine efficacy. Table 1 is introduced as a quick guide to current pharmacologic therapy with evidence of benefit in FM management to also be discussed further below (Table 1).

Gabapentinoids

Gabapentin and pregabalin are utilized for neuropathic pain, anxiety disorders, and partial seizures. They bind to neuronal voltage-gated calcium channels and decrease excitatory neurotransmitter release, thus decreasing neuronal excitability.[42] They also modulate GABAergic transmission. Pregabalin was the first US-FDA-approved medication for FM in 2007. A meta-analysis of clinical trial data showed pregabalin was effective at achieving 50% reduction in pain for 24% of patients, with similar and modest rates of adverse outcomes compared to placebo.[43] Pregabalin has been shown to be effective at improving sleep, pain, and function in patients with FM with a dose-response relationship for both pain relief and adverse events.[43,44] In the authors' practice, the authors generally start pregabalin at 75 mg twice daily and titrated up as needed and tolerated to a maximal dose of 450 mg/day.

Gabapentin is used with modest benefit for those patients who cannot tolerate pregabalin or who cannot afford the higher cost. Gabapentin reduces pain, improves sleep, and enhances health-related quality of life in some patients with FM.[45] The authors start it at a dose of 100-300 mg up to 3 times a day, but more typical effective treatment doses are in the range of 900-2400 mg/day in divided doses. Side effects of gabapentin and pregabalin include dizziness and somnolence.

Serotonin-Norepinephrine Reuptake Inhibitors

Milnacipran was approved in the US for the treatment of FM in 2009. Several studies using functional magnetic resonance imagery in FM have demonstrated that the drug increases blood flow to the areas of the brain involved in the descending inhibitory pain pathway.[46,47]

Table 1. Medications with Some Evidence for Efficacy in FM

Medication	Class	Starting Dose	Goal Dose	Common Side Effects[70]	Special Considerations[70]
Pregabalin	Gabapentinoid	75 mg twice daily	150 mg twice daily	Headache, dizziness, somnolence, nausea, dry mouth, weight gain	-United States Drug Enforcement Administration (DEA) schedule V; baseline creatinine; monitor for depression, suicidality; risk of Stevens-Johnson syndrome (SJS)
Gabapentin	Gabapentinoid	300 mg daily	300-800 mg three times a day	Headache, dizziness, somnolence, nausea, dry mouth, diarrhea, constipation	Baseline creatinine; monitor for depression, suicidality; risk of SJS
Milnacipran	SNRI	12.5 mg daily	50 mg twice daily	Headache, nausea, dry mouth, dizziness, palpitations	Risk of serotonin syndrome; baseline creatinine; risk of SJS
Duloxetine	SNRI	30 mg daily	60 mg daily	Headache, nausea, dry mouth, dizziness, weight loss	Risk of serotonin syndrome; baseline creatinine; risk of SJS
Cyclobenzaprine	Central-acting muscle relaxant	5 mg at night	10 mg at night	Headache, nausea, constipation, dry mouth, dizziness, somnolence, photosensitivity	Risk of cardiac conduction disturbance; caution if cardiac disease
Amitriptyline	TCA	10 mg at night	25-50 mg at night	Nausea, constipation, dry mouth, dizziness, somnolence, weakness, palpitations	Electrocardiogram if cardiovascular disease; risk of QT wave prolongation
Low-dose naltrexone	Opioid antagonist	4.5 mg daily	1-9 mg daily	Headache, nausea, constipation, dizziness, somnolence	Needs to be compounded at specialty pharmacy; monitor for depression, suicidality
Tramadol	Synthetic opioid	50 mg	50-100 mg every 6 hours prn	Headache, nausea, constipation, diarrhea, dizziness, somnolence	US-DEA schedule IV; risk of serotonin syndrome, SJS; baseline creatinine, monitor for resp depression and hypotension
Memantine	NMDAR antagonist	5 mg daily	10-30 mg daily divided twice daily	Dizziness, headache, constipation, diarrhea, somnolence, anxiety	Baseline creatinine; risk of SJS

Note that for FM no medications are yet approved by EMA, and only duloxetine, milnacipran, and pregabalin are approved by US FDA. NMDAR, N-methyl-D-aspartate receptor; SNRI, serotonin-norepinephrine reuptake inhibitor; TCA, tricyclic antidepressants.

An early open-label study found milnacipran to improve pain particularly in patients with comorbid depression.[48] In addition to pain benefits, studies found significant improvements in fatigue and other symptoms.[49] The authors have found milnacipran to be generally well-tolerated.

Duloxetine is the only SNRI besides milnacipran with substantial evidence to support use in FM as well as widespread pain in general. Venlafaxine has been used off-label in neuropathic pain and migraine prophylaxis, but evidence for benefit in FM is lacking. Duloxetine was licensed in the US for use in FM in 2008, and since then has become a mainstay of treatment of therapy, along with pregabalin and milnacipran. The authors start duloxetine at a dose of 30 mg daily and increase to 60 mg daily after a week if tolerated. It is a particularly good choice for patients with comorbid depression and/or anxiety.[50,51] One recent systematic review looked at 11 randomized clinical trials and concluded that duloxetine overall was of some benefit in improving symptoms of FM regardless of dose between 30 mg/day and 120 mg/day.[52]

A recent comprehensive review of 21 Cochrane reviews including 87 trials and 17 631 patients concluded that duloxetine, milnacipran, and pregabalin all showed, with moderate-to-good evidence, the ability to provide substantial pain relief for 1 out of every 10 adults with moderate-to-severe FM pain over a period of 4-12 weeks.[50] These conclusions are consistent with current use under FDA licensing. However, the European Medicines Agency (EMA) has yet to license any of these 3 choices for FM treatment.[50,53]

Cyclobenzaprine

Cyclobenzaprine (CBP) is a centrally acting muscle relaxant commonly used in FM. In randomized trials, CBP at doses ranging between 10 mg/day and 40 mg/day have shown global benefit as well as benefit for pain and sleep, with a significant side effect burden.[54,55] Our approach is to weigh response against emerging side effects. Many patients tolerate a 5-10 mg bedtime dose with some improvement in daytime pain, and this can be titrated up as tolerated.

Tricyclic Antidepressants

Tricyclic antidepressants are known to inhibit both serotonin and norepinephrine reuptake and improve pain at much lower doses than those used for depression. Amitriptyline has been an enduring choice for treatment of FM despite no good quality evidence for its benefit.[50,56] The starting dose is generally 10mg titrated up to 25-50 mg nightly.

Tramadol

Tramadol is a synthetic mu-opioid receptor agonist with serotonergic and noradrenergic properties as well as modulatory effects on myriad mediators involved in pain signaling.

It is thought to modify crosstalk between neuronal and non-neuronal cells in peripheral and central sites, thus modulating peripheral and central neuronal hyperexcitability.[57] It is often used in treatment of FM pain, and there have been few well-designed trials to assess the effectiveness. One review found that while Tramadol improved pain scores alone or in combination with other analgesics, the impact on quality of life did not hold up compared to placebo.[58] Another review in 2015 found there was fair evidence to support Tramadol as a second-line agent for FM pain.[59] While Tramadol is generally well tolerated, there is potential for dependence, as well as risk for serotonin syndrome when combined with other serotonergic agents. The dose is 50-100 mg every 6 hours. There is no evidence to support the use of stronger opioids for FM pain.

Low-Dose Naltrexone

Given FM involves central sensitization potentiated by neuroinflammation, additional pathways have been explored for therapeutic potential. Naltrexone is an opioid antagonist that is US-FDA approved for treatment of opioid and alcohol dependence with daily doses of 25-100 mg daily. Studies suggest low-dose naltrexone (LDN) in the range of 1-5 mg daily improves pain, possibly through analgesic and anti-inflammatory effects, modulating the endogenous opioid system, and neuroimmune modulatory roles. Low-dose naltrexone provides blockade of mu-, delta-, and kappa-opioid receptors, countering the increased opioid tone in patients with FM. A simultaneous antagonistic effect on microglial toll-like receptors 4 which are largely responsible for inflammatory and excitatory activity of these critical CNS dendritic cells may diminish some symptoms of FM, including sleep disturbances, cognitive dysfunction, fatigue, mood disorders, and increased nociception. This is essentially an anti-inflammatory, neuroprotective effect, with facilitation of endorphin function.[60]

Two different systematic reviews on LDN that included a subset of patients with FM found that LDN reduced FM-associated pain and improved quality of life and that LDN provided symptomatic improvement.[61,62] A subsequent review found that LDN therapy appears to be safe and effective for treatment of FM.[60] There is no consensus as to optimal dose, frequency, or duration of therapy as the data comes from case reports or smaller pilot trials. Doses range from 0.1 mg to 9 mg daily in these studies, with some doses divided twice daily, with 4.5 mg once daily being most common based on a dose response prospective trial.[63] Unfortunately, such a low dose of naltrexone is not available at commercial pharmacies and must be compounded. LDN is generally well tolerated.

N-Methyl-D-Aspartate Receptor Receptor Antagonists

As discussed, the NMDA receptor plays a significant role in FM pathophysiology. Studies have shown limited evidence for the NMDA receptor antagonists ketamine, dextromethorphan, and memantine with ketamine being the most widely studied. Ketamine for chronic pain has been limited by side effects and need for IV administration. Oral ketamine has not been extensively studied, with 1 study reporting meaningful response in a small proportion of patients.[21] Data is conflicting as to benefit for dextromethorphan, but use of memantine was supported by a preliminary trial of 63 patients with FM in Spain showing some significant improvement in pain as well as global functioning, quality of life, and mood.[21,64,65] The American Society of Anesthesiologists and the American Society of Regional Anesthesia and Pain Medicine support the use of NMDA receptor antagonists for neuropathic pain based on multiple studies but additional work is needed.[66,67] Memantine is used for Alzheimer's disease as well as for migraine prophylaxis and is generally well-tolerated. The starting dose is usually 5 mg daily, increasing weekly by 5 mg up to 20 mg daily in divided doses.

Nonsteroidal Anti-Inflammatory Drugs

Nonsteroidal anti-inflammatory drugs (NSAIDs), both oral and topical, are used in FM as adjuncts. Their use is limited by consideration of risk to the gastrointestinal and genitourinary systems, more so for oral agents. A 2017 Cochrane Review found no reliable evidence supporting a recommendation for use of NSAIDs in FM.[50] The authors generally avoid using NSAIDs in patients with FM unless there is a more overtly inflammatory disorder present as well, as is so often the case.

Acetaminophen (Paracetamol)

There is no strong evidence that acetaminophen is effective in the treatment of FM, and it is not recommended alone or as a first-line agent. Given the general safety profile and some evidence of efficacy in combination with tramadol, it can be considered as an adjunctive medication.[68]

Selective Serotonin Reuptake Inhibitors

Selective serotonin reuptake inhibitors (SSRIs) have not been found to be effective in the management of the core symptoms of FM but may be considered to treat comorbid anxiety and depression symptoms.[50] In patients with FM who also have significant mood disorders extant or emerging, the authors prefer to start with duloxetine as first-line therapy given its clear indication for major depressive disorder and generalized anxiety disorder. The exception would be for a patient who is already on an SSRI or TCA from which they are benefitting, in which case the preferred first-line agent to treat the FM would be a gabapentinoid.

Treatment of Comorbid Diseases

All patients who have OSA concurrent with FM should be managed by a sleep medicine specialist. The modalities of care are beyond the scope of this review, but the authors will note it is generally accepted that FM symptoms improve to some extent when a patient is effectively treated for comorbid OSA. In many cases, as the authors have discussed, sleep disorders commonly underpin many symptoms of FM.

A recent development in the US is FDA approval of the glucose-dependent insulinotropic polypeptide receptor agonist tirzepatide for treatment of OSA in patients with obesity, just 1 year after its approval for treatment of obesity alone. Given the incidence of OSA and obesity comorbid with FM, the authors find this to be a hopeful step toward improving FM symptoms in these patients and are looking forward to studies of tirzepatide in FM comorbid with obesity with or without OSA.

Conclusion

Fibromyalgia has challenged the medical community for decades with a complex constellation of symptoms. Gradual elucidation of pathophysiology has revealed an inflammatory component potentiating central sensitization among other pathology. The debate continues as to whether there is also an autoimmune underpinning, with a recent review presenting an elegant argument on each side.[69] The present discussion of pathophysiology points to potential mechanistic underpinnings of some variably successful therapies, most notably SNRIs, gabapentinoids, memantine, and LDN. Correlated also are known pathologic characteristics, such as parallel inflammation identified in patients with FM as well as those with obesity or both conditions, with potential future therapies such as the glucose-dependent insulinotropic polypeptide receptor agonists to address the inflammatory component extant in both diseases. Also underscored is the importance of non-pharmacologic treatment as the keystone of successful therapy, especially improvements in sleep and physical

activity, while endorsing benefit of complementary and alternative measures such as education, acupuncture, yoga, and PRT.

With FM and similar pain conditions receiving increased attention, it is hoped that an improved understanding of pathophysiology, with eventual organization of differing presentations into phenotypic categories, along with increased emphasis on multifaceted and multidisciplinary treatment, will reduce the global burden of this debilitating disease.

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